REMARKS

Claims 31-41 and 46-62 are pending in this application with claims 46 and 47 being withdrawn. After entry of this paper, claims 31-41 and 46-62 will remain pending and are presented for consideration.

Rejections Under 35 U.S.C. § 103(a)

Claims 31-41, 48-53, 56-60 and 62 stand rejected under 35 U.S.C. § 103(a) over Favaloro *et al.*, (Pathology, 25:152-158 (1993) ("Favaloro")) in view of Vischer *et al.* (Critical Reviews in Oncology/Hematology, 30:93-109 (1999) ("Vischer")), in view of Hoylaerts *et al.* (Biochem. J. 386:453-463 (1995) ("Hoylaerts")), and in view of Handin (U.S. Patent No. 5,321,127 ("Handin")). Claim 54 stands rejected under 35 U.S.C. § 103(a) further in view of Batz *et al.* (U.S. Patent No. 4,415,700 "Batz"). Claim 55 stands rejected under 35 U.S.C. § 103(a) further in view of Solen *et al.* (U.S. Patent No. 6,043,871 "Solen"). Claim 61 stands rejected under 35 U.S.C. § 103(a) further in view of Vicente (J. Biol. Chem., 263:18473-18479 (1988) ("Vicente")). Applicants traverse the rejections for the reasons set forth below.

Applicants' Claimed Invention

Applicants' claimed invention is directed to a method for detecting von-Willebrand's disease by, *inter alia*, detecting a binding activity of von-Willebrand's factor (vWF) in a sample, determining an amount of vWF-antigen in the sample, determining a ratio between the binding activity and the amount of vWF-antigen, comparing the ratio to a reference range and detecting von-Willebrand's disease based on the comparison.

According to Applicants' claimed invention, the binding activity detected is the binding activity of vWF in a sample to a soluble form or a portion of GP1b(α) that is not associated with a platelet in the presence of ristocetin or a functionally equivalent substance.

Prior to Applicants' claimed invention, no one had successfully used a soluble form or portion of GP1b(α), such as glycocalicin or any other soluble fragment of GP1b(α), to detect von-Willebrand's disease based on the binding activity between the vWF and the soluble fragment of GP1b(α). Applicants discovered for the first time that such a soluble fragment can

be successfully used to detect von-Willebrand's disease using the method described and claimed in the present application.

Based on the arguments presented in the response filed on February 22, 2007, and for the reasons set forth below, Applicants respectfully submit that the claimed invention is not obvious and therefore patentable.

The Examiner, at pages 5-6 of the Office action, suggests that Favoloro teaches a method for detecting von-Willebrand's disease according to Applicants' claimed invention but for the fact that Favaloro fails to teach the claimed step of detecting a binding activity of vWF in a sample to a soluble form or a portion of glycoprotein 1b(α) that is not associated with a platelet in the presence of ristocetin or a functionally equivalent substance.

Given the deficiencies of Favoloro, the Examiner suggests that the teachings of Favoloro should be combined with the teachings of Vischer, Hoylaerts, and Handin to arrive at Applicants claimed invention. Applicants respectfully submit that none of Vischer, Hoylaerts, or Handin cures the deficiencies of Favoloro.

Favoloro, Vischer, and Hoylaerts

Vischer teaches that von-Willebrand's disease is a heterogeneous disease having many types (see, *e.g.*, page 99, table 2). For example, Vischer teaches that Type 2 von-Willebrand's disease refers to a qualitative vWF deficiency (page 99, table 2). Vischer further teaches that type 2 von-Willebrand's disease can be detected by a collagen binding assay (page 102, left hand col.). Vischer acknowledges that Type 2 von-Willebrand's disease has several subtypes. Vischer teaches that type 2B von-Willebrand's disease can be detected by increased platelet agglutination at low concentrations of ristocetin (page 100, left hand col.).

Hoylaerts teaches the isolation of the GP1b protein from platelets (page 454, left hand column, paragraph 2). Hoylaerts uses the isolated GP1b protein in an ELISA method to analyze how ristocetin mediates the binding of vWF to isolated GP1b (page 454, left hand col.). Hoylaerts is deficient in that he does not teach a soluble form of GP1bα. Further, Hoylaerts is silent as to the isolated GP1b being used to make a diagnosis of von-Willebrand's disease.

The Examiner suggests that Vischer provides a motivation to employ the assay of Hoylaerts in addition to the collagen binding assay of Favoloro in order to differentiate type 2B and type 2A von-Willebrand's disease (Office action, page 11, lines 4-9). Applicants' respectfully disagree.

Firstly, Applicants submit that Hoylaerts does not teach that Hoylaerts' method is capable of detecting von-Willebrand's disease, let alone type 2A or 2B von-Willebrand's disease. Accordingly, Applicants fail to see why a skilled artisan would use Hoylaert's method in conjunction with Favoloro's method in order to differentiate type 2B and type 2A von-Willebrand's disease.

Secondly, for the sake of argument, even if Hoylaert's method detected type 2B von-Willebrand's disease by increased platelet agglutination at low concentrations of ristocetin as taught by Vischer, which Applicants' submit Hoylaerts does not, Applicants fail to see how employing both Favoloro's collagen binding assay and Hoylaert's method would allow differentiation between type 2B and 2A von-Willebrand's disease as suggested by the Examiner at page 11 of the Office action. In particular, as described above, Vischer teaches that type 2 von-Willebrand's disease can be detected by a collagen binding assay (page 103, left hand col.). However, Vischer does not teach that the collagen binding assay allows detection of any particular subtype of type 2 von-Willebrand's disease, *e.g.*, type 2A von-Willebrand's disease. Accordingly, while Vischer teaches that Type 2B von-Willebrand's disease can be detected by increased platelet agglutination at low concentrations of ristocetin (page 100, left hand col.), there is no teaching in Vischer, Hoylaerts, or Favoloro that indicates one can detect type 2A von-Willebrand's disease with either of Hoylaerts' assay or Favoloro's collagen binding assay. Accordingly, Applicants' submit that the Examiner's motivation for combining the teachings of Favoloro, Hoylaerts, and Vischer is flawed.

The Examiner further supports the combination of Favoloro, Vischer, and Hoylaerts stating that "it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose" (Office action, page 11, citing *In re Kerkhoven*, 626 F.2d 846 at 850 (CCPA 1980)). Applicants submit that the Examiner's application of this case to the facts is incorrect.

Applicants submit that *In re Kerkhoven* stands for the proposition that "[i]t is *prima facie* obvious to combine two compositions each of which is known in the art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose." *In re Kerkhoven* at 850 (emphasis added). If the Examiner is asserting that the assays of Favoloro and Hoylaerts should be combined to create a third assay, such a combination is not supported by the rationale of *In re Kerkhoven.*

As stated therein, the combination of elements must be used for the very same purpose. Applicants submit that neither the assay of Favoloro or Hoylaerts is used for the very same purpose. For example, as asserted by the Examiner, Favoloro teaches a collagen binding assay (Office action, pages 10-11). As stated in the Declaration of Dr. Hans Deckmyn, filed in this application on February 22, 2007, the collagen binding assay for detecting vWF "primarily involves the functional domain A3 of mature vWF" ("Deckmyn Declaration," page 3, paragraph 7b). In contrast, binding of vWF to the GP1b complex involves functional domain A1 of vWF (Deckmyn Declaration, page 3, paragraph 7b). Accordingly, the purposes of the collagen binding assay and an assay detecting vWF/GP1b binding are different, namely to detect defects in differing functional domains of vWF. As such, these assays cannot be combined under the rationale of *In re Kerkhoven* to form a third assay as the Examiner suggests.

Even if, *arguendo*, the rationale of *In re Kerkhoven* did apply to make obvious a third assay combining the assays of Favoloro and Hoylaerts, Applicants submit that the Examiner has provided no rationale as to why a third assay comprising the Favoloro and Hoylaerts methods would function for any purpose.

In addition, even if there were a motivation to combine the teachings of Favoloro, Vischer, and Hoylaerts, Applicants submit that a skilled artisan would have no reasonable expectation of success at detecting von-Willebrand's disease using the method of Hoylaerts. Hoylaerts is silent as to whether Hoylaerts' ELISA method for demonstrating the ristocetin mediated binding of vWF to GP1b can be used to diagnose von-Willebrand's disease. Applicants' claimed invention is a method for detecting von-Willebrand's disease and recites a step of detecting von-Willebrand's disease. Hoylaerts provides no indication that the binding

activity between vWF and Hoylaerts' GP1b in the absence of platelets would provide data sufficient for making a diagnosis of von-Willebrand's disease.

In fact, it is known in the art that the binding of vWF to GP1b is mediated by carbodydrate sidechains clustered near the boundaries of the A1 domain of vWF (Vischer, page 95, left hand col.). Applicants submit that there is no evidence in the prior art references of record to indicate that isolated GP1b, absent a platelet, would bind to vWF with the same affinity as when GP1b is associated with a platelet. In other words, Applicants submit that there is no evidence that binding of isolated GP1b with vWF permits the appropriate conformation of carbohydrate side chains of vWF that occurs when binding with platelet associated GP1b.

Handin

The Examiner suggests that Handin teaches soluble GP1bα (Office action, page 11, lines 12-15). The Examiner suggests that it would have been obvious to one of ordinary skill in the art to use Handin's soluble GP1bα in Hoylaert's ELISA method in place of Hoylaert's GP1b protein because GP1b contains components that are allegedly not involved in the specific binding activity of vWF, while Handin's GP1bα allegedly contains the ristocetin-dependent vWF binding site.

Applicants' submit that a skilled artisan would have no motivation to use Handin's GP1bα fragment in Hoylaert's assay to arrive at Applicants' claimed method of detecting von-Willebrand's disease because Handin does not teach measuring the binding activity of vWF in a sample to a soluble form of GP1b(α) that is not associated with a platelet. Rather, Handin teaches that soluble GP1b(α) fragments such as glycocalicin or rGp1bαQ221-L318 inhibit ristocetin-dependent binding of vWF to platelets and teaches an assay to demonstrate such inhibition ability of glycocalicin or rGp1bαQ221-L318. For example, as set forth in column 15, line 52, to column 16, line 3, Handin teaches: "The ability of recombinant GP1bα (rGP1bα) to inhibit ristocetin-dependent binding of [^{125}I]-vWF to platelets was assessed with *paraformaldehyde-fixed platelets*. . . . The ability of purified [glycocalicin] or the rGP1bα polypeptides to block vWF binding was assessed by adding increasing concentrations of the appropriate test substance to the assay mixture" (emphasis added).

Therefore, Handin teaches a platelet aggregation assay that uses a soluble fragment of GP1b(α) such as glycocalicin or rGp1bαQ221-L318 to measure its ability to inhibit vWF binding to *platelets*, not to measure the binding activity of vWF in a sample to the soluble fragment of GP1b(α) that is not associated with a platelet. In fact, Handin does not teach any assay to detect the binding activity of vWF in a sample to a soluble fragment of GP1b(α). Moreover, Handin is silent with respect to the application of a soluble fragment of GP1b(α) to detect von Willebrand's disease.

Further, Applicants' submit that a skilled artisan would have no reasonable expectation of success in using any of Handin's soluble fragments of GP1b(α) in the assay of Hoylaert's to accurately detect the binding activity of vWF in a sample to a soluble form of GP1b(α). For example, Handin teaches that "[n]one of the recombinant polypeptides analyzed...contained the serine threonine-rich region to which O-linked oligosaccharides are attached" (col. 18, lines 45-47). In other words, Handin's recombinant GP1b(α) fragments were devoid of O-linked oligosaccharides. Given that a skilled artisan is aware that glycosylation patterns can be involved in protein-protein binding, Applicants submit that the absence of O-linked oligosaccharides from Handin's recombinant GP1b(α) fragments would preclude a skilled artisan from having a reasonable expectation of success at using those fragments to obtain appropriate levels of binding to vWF necessary for a diagnosis of von-Willebrand's disease.

Even though Handin teaches that the biologic activity of rGpIbαL318, one recombinant GP1b(α) fragment, had the same biological activity as glycocalicin, a larger, glycosylated proteolytic fragment of GP1b, Handin measured the biological activity of the fragment by inhibition of ristocetin-dependent binding of vWF to *platelets*, not by determining the binding activity of vWF to the soluble GP1b(α) fragment (col. 18, lines 48-52). Accordingly, Applicants' submit that Handin's observation regarding the biologic activity of rGpIbαL318 is irrelevant to the effects of those glycosylation patterns on the binding activity of vWF to soluble GP1b(α) as useful for an assay for detecting von-Willebrand's disease.

Accordingly, Applicants submit that even if a skilled artisan had a motivation to use a soluble fragment of GP1b(α) of Handin in the assay of Hoylaerts, a skilled artisan would not have a reasonable expectation that using any of the recombinant GP1b(α) fragments of Handin

would produce the requisite biological activity to provide an accurate measurement of vWF binding activity in the sample necessary for making a correct diagnosis of von Willenbrand's disease.

Moreover, Handin provides no indication that the binding activity between vWF and Handin's GP1b(α) fragments in the absence of platelets would provide data sufficient for making a diagnosis of von-Willebrand's disease. Accordingly, Applicants submit that a skilled artisan would have no reasonable expectation that using any of the recombinant GP1b(α) fragments of Handin would produce the requisite biological activity to provide an accurate measurement of vWF binding activity in the sample necessary for making a correct diagnosis of von Willenbrand's disease.

In addition, Applicants submit that a skilled artisan would have no motivation or reasonable expectation of success in using the soluble GP1b(α) fragments of Handin to replace GP1b in the method taught by Hoylaerts because the prior art, discussed below, indicates that the binding activity between vWF and soluble GP1b(α) is not robust enough to provide clinically relevant test data to allow accurate discrimination between normal samples and samples from patients with von Willebrand's diseases.

Christophe, cited by the Examiner in the October 23, 2006, Office action, addresses this point. Christophe compared the binding capacity of plasma vWF from type 2 (*i.e.*, type II) von Willebrand's disease patients and normal controls to a soluble fragment of GP1b(α) glycocalicin and to platelet GP1b (see, Christophe, page 3554, left column). Christophe found that, while ristocetin-induced binding of plasma vWF to fixed platelets correlated with the clinical phenotypes of type 2 von Willebrand's disease, the binding of plasma vWF from type 2 von Willebrand's disease patients to glycocalicin is normal (see, Christophe, Figure 6, Table 1 and page 3557, right column and page 3560, left column). In other words, Christophe disclosed that the binding activity between vWF in a plasma sample and a soluble fragment of GP1b(α) glycocalicin detected in its experiment did not provide clinically relevant data to allow discrimination between normal samples and samples from patients with von Willebrand's diseases. Therefore, one of skill in the art in view of the teachings in Christophe would have been discouraged from using a soluble fragment of GP1b(α), such as fragments taught by

Handin, instead of platelets to detect von Willebrand's disease. One of skill in the art in view of the teachings in Christophe also would not have expected that a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease based on its binding activity to vWF in a sample.

Batz, Solen, and Vicente

Similarly, none of the other references cited by the Examiner teach or suggest that a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease based on its binding activity to vWF in a sample. As discussed previously, Favaloro teaches a method for detecting von Willebrand's disease using a collagen-binding assay. Hoylaerts teaches use of an ELISA method to study how ristocetin mediates the binding of vWF to the GP1b complex (*see, e.g.*, Hoylaerts, page 454, left column, first paragraph). Batz teaches use of hydrophilic latex particles as carrier materials for biological and/or immunologically active substances in diagnostic agents (*see, e.g.*, Batz, abstract and the first paragraph in detailed description). Solen teaches a system and a method for measuring the platelet aggregation in whole blood in response to standard aggregating agents (*see, e.g.*, Solen, abstract). Vicente teaches a 45 KDa GP1b(α) N-terminal fragment of GP1b(α) (glycocalicin) that is capable of interacting with purified surface-bound vWF (*see, e.g.*, Vicente, abstract, page 18475, left column). Therefore, not one of the cited references teach or suggest that a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease based on its binding activity to vWF in a sample.

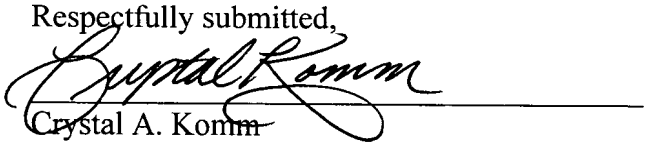
Indeed, despite the fact that it had been known since 1988 that a soluble fragment of GP1b(α) glycocalicin is capable of binding to vWF, no one had successfully used glycocalicin or any other soluble fragment of GP1b(α) to detect von Willebrand's disease based on the binding activity between the vWF and the soluble fragment of GP1b(α) prior to Applicants' invention. Applicants discovered for the first time that such a soluble fragment can be successfully used to detect von Willebrand's disease using the method described and claimed in the present application. Accordingly, Applicants submit that their invention for a method for detecting von Willebrand's disease using a soluble fragment of GP1b(α) is not obvious.

Applicants therefore respectfully submit that claim 31 and claims 32-41 and 48-62 dependent therefrom are novel and unobvious over Favaloro, Christophe, Handin, Hoylaerts, Batz, Solen, and Vincent for all the foregoing reasons. Applicants therefore respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

CONCLUSION

Applicants believe that the pending claims are now in condition for allowance. The Examiner is invited to telephone the undersigned attorney to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,



Dated: November 20, 2007
Limited Recognition No.: L0363

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